Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study

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Abstract: BRAF and MEK kinase inhibitors can be highly effective in treating BRAF-mutant melanomas, but their safety and activity in patients with active/symptomatic brain metastases are unclear. We sought to shed light on this open clinical question. We conducted a multicenter retrospective study on real-life patients with melanoma and active brain metastases treated with combination BRAF/MEK inhibitors. A total of 65 patients were included (38 men and 27 women; median age: 49 years). Of them, 53 patients received dabrafenib/trametinib, 10 received vemurafenib/cobimetinib, one received encorafenib/binimetinib, and one received vemurafenib/trametinib. We did not observe any unexpected treatment-related safety signals in our cohort. Overall, 17 patients continued on therapy through the cutoff date. After initiation of therapy, steroid dose could be decreased in 22 of 33 patients (11 tapered off entirely), anticonvulsants were stopped in four of 21, and narcotics were stopped in four of 12. Median progression-free survival from the start of therapy was 5.3 months (95% confidence interval: 3.6-6.1), and median overall survival was 9.5 months (95% confidence interval: 7.7-13.5). A total of 20 patients were surviving at the cutoff date. Univariate analysis of age, sex, ulceration status, thickness, stage, location, or lactate dehydrogenase did not reveal significant predictors of progression-free survival or overall survival within our cohort, but multivariate analysis suggested that older age, lower risk location of original lesion, and nodular melanoma are poor prognostic indicators. Combination therapy with BRAF/MEK inhibitors is a viable treatment option for patients with BRAF-mutant melanoma and brain metastases, but further studies should help to define the optimal treatment approach in this population.

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BRAF and MEK kinase inhibitors can be highly effective in treating *BRAF*-mutant melanomas, but their safety and activity in patients with active/symptomatic brain metastases are unclear. We sought to shed light on this open clinical question. We conducted a multicenter retrospective study on real-life patients with melanoma and active brain metastases treated with combination BRAF/MEK inhibitors. A total of 65 patients were included (38 men and 27 women; median age: 49 years). Of them, 53 patients received dabrafenib/trametinib, 10 received vemurafenib/cobimetinib, one received encorafenib/binimetinib, and one received vemurafenib/trametinib. We did not observe any unexpected treatment-related safety signals in our cohort. Overall, 17 patients continued on therapy through the cutoff date. After initiation of therapy, steroid dose could be decreased in 22 of 33 patients (11 tapered off entirely), anticonvulsants were stopped in four of 21, and narcotics were stopped in four of 12. Median progression-free survival from the start of therapy was 5.3 months (95% confidence interval: 3.6–6.1), and median overall survival was 9.5 months (95% confidence interval: 7.7–13.5). A total of 20 patients were surviving at the cutoff date. Univariate analysis of age, sex, ulceration status, thickness, stage, location, or lactate dehydrogenase did not reveal significant predictors of progression-free survival or overall survival within our cohort, but multivariate analysis suggested that older age, lower risk location of original lesion, and nodular melanoma are poor prognostic indicators. Combination therapy with BRAF/MEK inhibitors is a viable treatment option for patients with *BRAF*-mutant melanoma and brain metastases, but further studies should help to define the optimal treatment approach in this population. *Melanoma Res* 29:65–69

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Introduction

Melanoma accounts for less than 1% of skin cancer diagnoses but causes the overwhelming majority of skin cancer-related deaths. The incidence of melanoma has risen over the past 30 years, and estimates predicted more than 87 000 new cases and nearly 10 000 deaths occurred in 2017 in the USA alone [1]. Treatment for many patients with invasive melanoma was transformed with the discovery of mutations in the *BRAF* gene, which occur in an estimated 50% of cutaneous melanomas, and it drove cell growth and division by the mitogen-activate protein kinase signaling pathway [2]. Greater than 80% of *BRAF* mutations are caused by a T1799A transversion in exon 15, resulting in the substitution V600E (Val600Glu). Clinically, *BRAF* mutations are associated with younger age, location of original lesion on the trunk, lack of chronically sun-damaged skin, and aggressive disease with advanced melanoma stage at presentation [3]. Among all cancers, melanoma is the third most common cause of brain metastasis (after lung and breast) [4]. Approximately 7% of patients with melanoma are found to have brain metastasis at diagnosis, and 40–50% of patients with stage IV melanoma develop brain metastases at some point in their disease course; indeed *BRAF* mutations may predispose patients to developing brain metastases [5,6]. Brain involvement is associated with poor prognosis, including an estimated 43% 3-month survival, as well as a high degree of morbidity and cost [7].

Several therapies targeting BRAF are currently in use or under investigation for the treatment of *BRAF*-mutant metastatic melanoma, including vemurafenib [approved by the Food and Drug Administration (FDA) in 2011], dabrafenib (FDA approved in 2013), and encorafenib (FDA approval pending) [8–10]. More recently, BRAF inhibitors are co-administered with inhibitors of MEK,

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another kinase downstream of BRAF in the same signaling pathway. Combination therapy of BRAF inhibitors with the MEK inhibitors trametinib (FDA approved in 2013), cobimetinib (FDA approved in 2015), and binimetinib (FDA approval pending), improves survival over monotherapy with BRAF inhibitors alone [11–14].

The clinical development of BRAF inhibitors with or without MEK inhibitors was largely limited to patients who did not have active brain metastases, and thus the role of BRAF-targeted therapy in patients with brain metastases is not yet fully understood. One other recent retrospective study showed a median overall survival of 6.6 months, median intracranial progression-free survival (PFS) of 4.2 months, and intracranial radiologic response rate of 63% for patients with symptomatic brain metastases [15]. Early-phase trials show promising signs of intracranial efficacy, including response rates of 20–40% with dabrafenib, and 40% with vemurafenib; ongoing prospective trials are just beginning to reach the literature [16–18]. For example, the COMBI-MB study recently prospectively investigated the use of dabrafenib plus trametinib in patients with melanoma and brain metastases, finding a median PFS of 5.6 months, and a median overall survival (OS) of 10.8 months [19]. However, prognostic data from clinical trials may not be perfectly representative owing to selection bias in trial participants [20]. To contribute to the developing data on this patient population, we present our multicenter experience treating real-life patients with melanoma brain metastases with combination BRAF/MEK-inhibitor therapy.

Patients and methods

The objective of this study was to characterize the clinical course of patients with *BRAF*-mutated metastatic melanoma and brain metastases who received combination BRAF and MEK targeted therapy (BRAF/MEK-I). To merit inclusion, patients were required to have biopsy-proven melanoma with brain metastases harboring a *BRAF* mutation at the V600 position, and to have received combination BRAF/MEK-I therapy between 2013 and the data cutoff date of 25 October 2016, at one of our five clinical centers. Retrospective chart review was performed on all patients to obtain data concerning features of patients' initial melanoma diagnosis, symptomatic response to therapy, treatment interruptions/adverse events, time to progression, and overall survival.

Statistical analysis

Demographic and disease characteristics, patient status, and treatment are summarized descriptively. OS is defined as the time from the start of BRAF inhibitor to death from any cause, and patients who did not die are censored at the date last known alive. PFS is defined as the time from the start of BRAF inhibitor to progression or death from any cause, and patients who did not progress or die are censored at the date last known alive. Several patients started combination therapy in a staggered fashion, starting with BRAF inhibitor before the initiation of a MEK inhibitor. This occurred when access to trametinib was limited to compassionate use at European sites. The distributions of survival are presented using the method of Kaplan–Meier along with the 95% confidence interval (CI). The 95% CI of the median survival times are estimated using log[− log(endpoint)] methodology. Multivariable Cox models are fit using backward, forward, and stepwise selection to assess model consistency. Candidate predictors in the models are age (divided at 49 years), Breslow thickness (0.1–2, 2.01–4, > 4 mm, and unknown), ulceration (no, yes, and unknown), location (higher risk, lower risk, other, and unknown), type of melanoma (superficial spreading, nodular, other, and unknown), and lactate dehydrogenase at treatment start (normal, abnormal, and unknown). Hazard ratios are presented with 95% Wald CIs. Statistical significance is defined as P less than or equal to 0.05.

Results

Patient demographics

We identified 65 patients who met the inclusion criteria for the analysis. Of them, 26 (40.0%) were treated at Massachusetts General Hospital, 25 (38.5%) were treated at Essen, 10 (15.4%) were treated at Zurich, two (3.1%) were treated at St Gallen, and two (3.1%) were treated at Basel. The median (95% CI) follow-up duration was 19 (16–31) months. Demographic data are summarized in Table 1.

Treatment regimens and previous therapies

A total of 53 (81.5%) patients received dabrafenib/trametinib, 10 (15.4%) received vemurafenib/cobimetinib, one received encorafenib and binimetinib, and one received vemurafenib and trametinib. Forty-four (67.7%) patients received systemic therapy before the initiation of BRAF/MEK inhibitors. Twelve (18.5%) patients started combination therapy in a staggered fashion, starting with BRAF inhibitor a median of 16.5 days before the initiation of a MEK inhibitor. Eighteen (27.7%) had received before anti-CTLA-4 therapy, 12 (18.5%) received before anti-PD1 therapy, 13 (20%) received previous adjuvant interferon, and three (4.6%) received previous chemotherapy. Eighteen (27.7%) underwent brain surgery before the treatment start, 22 (33.8%) underwent stereotactic radiosurgery, and 20 (33.3%) underwent whole-brain radiation.

Treatment toxicity and adverse events

Seventeen (26.2%) patients remained on therapy through data cutoff date. Seven (10.8%) patients required dose reductions, six of which were because of fever. Twenty-two (33.8%) patients had treatment interruptions, which lasted for an average of 23.5 days. Interruption occurred owing to fever [14 (63.6%) interruptions], radiation

therapy ($n=4$), infection ($n=2$), and hepatitis/abnormal liver function tests ($n=2$). Forty-eight (73.8%) patients discontinued therapy entirely, 33 (68.8% of discontinuations) because of disease progression, and 10 (20.8%) because of adverse events. Of the 10 patients who stopped therapy owing to adverse events, fever was the principal reason in eight cases, and abnormal liver function tests accounted for the other two.

In the overall study population, the most common adverse event was fever, which occurred in 13 (20%) patients. Nine (13.8%) patients had a rash, seven (10.8%) had fatigue, six (9.2%) had CK elevation/myositis, six (9.2%) had infection, five (7.7%) had diarrhea, four (6.2%) had abnormal liver function tests, three (4.6%) had fevers, three (4.6%) had thrombosis, two (3.1%) had palpitations, two (3.1%) had nausea, and two (3.1%) had hypertension. Only one patient experienced each of the following: ocular complications, dizziness, alopecia, central nervous system bleed, and myocardial infarction.

Symptomatic response

The most common neurologic symptoms that patients noted at baseline were headaches [18 (27.7%)] and motor symptoms such as paralysis [18 (27.7%)]. Ten (15.4%) had a documented history of sensory disturbance, and seven (10.8%) had seizures. Thirty-three (50.8%) patients were taking steroids at the start of BRAF inhibitor therapy, of which 22 (66.7% of those on steroids) were able to decrease their steroid dose after starting therapy, and 11 (33.3% of those on steroids) were able to taper off steroids. Twenty-one (32.3%) were taking anticonvulsants at treatment start, and four (19% of those on anticonvulsants) tapered off therapy. Twelve (18.5%) were taking narcotic pain medications at treatment start, and four (33.3% of those on narcotics) could discontinue after treatment commencement (Table 2).

Survival analyses

At the data cutoff date, 57 (87.7%) patients exhibited disease progression, and 45 (69.2%) patients had died. Median progression-free survival from start of BRAF/MEK inhibitor was 5.3 months (95% CI: 3.6–6.1). Median overall survival from start of BRAF/MEK inhibitor therapy was 9.5 months (95% CI: 7.7–13.5), as shown in Figs 1 and 2. Univariate analysis of all presented demographic variables did not reveal significant predictors of survival within our cohort.

Multivariate analysis revealed that overall survival was significantly related to age, location, and type of melanoma. Holding other predictors constant, patients older than 49 years had hazards of death that were more than

Table 1 Baseline patient characteristics

Characteristics	*n* (%)
Age at first diagnosis [median (min–max)] (years)	49.2 (16.2–72.2)
Sex	
Female	27 (41.5)
Male	38 (58.5)
Group	
European cohort	39 (60)
American cohort	26 (40)
UICC-stage at first diagnosis	
Breslow ≤ 2 mm	16 (24.6)
2–4 mm	16 (24.6)
LN or in transit	15 (23.1)
Distant mets	15 (23.1)
Unknown	3 (4.6)
Location of primary lesion	
Lower risk (upper or lower extremity)	12 (18.5)
Higher risk (head/neck or torso)	35 (53.8)
Other	4 (6.2)
Unknown	14 (21.5)
Type of melanoma	
Superficial spreading	14 (21.5)
Nodular	18 (27.7)
Other	5 (7.7)
Unknown	28 (43.1)
De-novo metastatic disease	
Yes	15 (23.1)
No	50 (76.9)
LDH at treatment start	
Normal	26 (40.0)
Abnormal	31 (47.7)
Unknown	8 (12.3)
Immunotherapy before BRAF/MEK-I	
Anti-PD1	18 (27.7)
Anti-CTLA-4	12 (18.5)
BRAF/MEK-I received	
Dabrafenib/trametinib	53 (81.5)
Vemurafenib/cobimetinib	10 (15.4)
Other	2 (3.1)

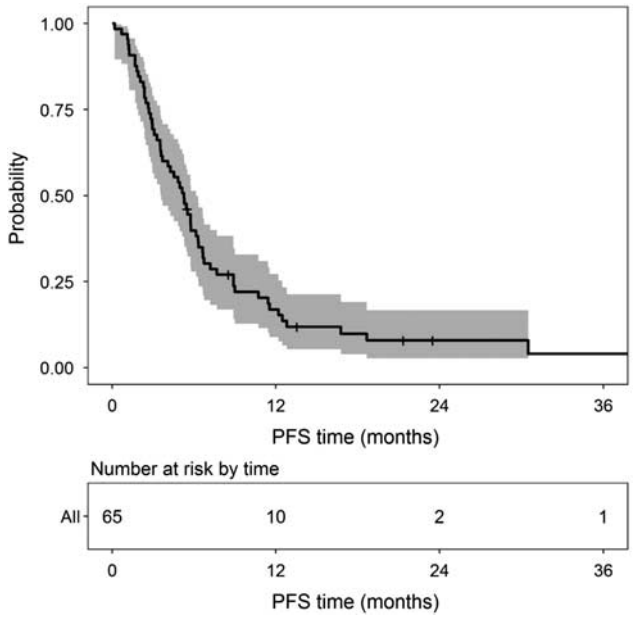
BRAF/MEK-I, BRAF/MEK inhibitor; LDH, lactate dehydrogenase; LN, lymph nodes; max, maximum; min, minimum.

Table 2 Clinical outcomes

Outcomes	*n* (%)
Steroid response	
Taking steroids at treatment start	33
Steroid dose reduction after treatment	22 (66.7)
Steroid discontinuation after treatment	11 (33.3)
Anticonvulsant response	
Taking anticonvulsants at treatment start	21
Anticonvulsant dose reduction after treatment	4 (19)
Anticonvulsant discontinuation after treatment	0 (0)
Opioid response	
Taking opioids at treatment start	12
Opioid dose reduction after treatment	4 (33)
Opioid discontinuation after treatment	4 (33)
Adverse events (>5% prevalence)	
Fever	13 (20)
Rash	9 (13.8)
Fatigue	7 (10.8)
CK elevation/myositis	6 (9.2)
Infection	6 (9.2)
LFT abnormalities/hepatitis	4 (6.2)
Therapy discontinuation	
Total discontinuation events	48
Discontinuation due to progression of disease	33 (68.8)
Discontinuation due to adverse event	10 (20.8)
Other	5 (10.4)
Mortality at study close	
Alive	20 (30.8)
Dead	45 (69.2)
Progression at study close	
No progression	7 (10.8)
Progression	57 (87.7)
Unknown	1 (1.5)

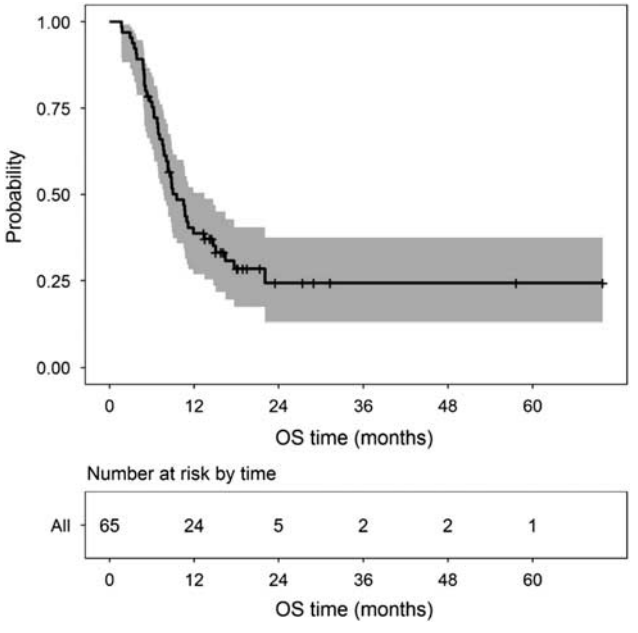
CK, creatine kinase; LFT, liver function test.

Fig. 1



Progression-free survival (PFS). Median progression-free survival from start of BRAF/MEK-inhibitor was 5.3 months (95% confidence interval: 3.6–6.1).

Fig. 2



Overall survival (OS). Median overall survival from start of BRAF/MEK-inhibitor therapy was 9.5 months (95% confidence interval: 7.7–13.5).

double those of patients younger than 49 years [hazard ratio (HR): 2.18, 95% CI: 1.09–4.37; $P=0.03$]. The hazards of death for patients with lower risk location (upper or lower extremity) increased more than three times (HR: 3.32, 95% CI: 1.48–7.46; $P=0.01$) compared with patients with higher risk location (head/neck or torso) while holding other covariates constant. Finally, the hazards of death for patients with nodular melanoma increased almost five times (HR: 4.95, 95% CI: 1.92–12.75; $P=0.01$) compared with patients with spreading melanoma while holding other covariates constant.

Discussion

Targeted therapy with BRAF/MEK inhibitors is a feasible treatment paradigm and alternative to immunotherapy in patients with *BRAF*-mutant melanoma with brain metastases. Despite that, the presence of brain metastases in metastatic melanoma is still a devastating diagnosis with a median PFS of 5.3 months, and a median OS of 9.5 months in our cohort. Our results align closely with the prospective COMBI-MB trial that reported a median PFS of 5.6 months and a median OS of 10.8 months for patients taking dabrafenib plus trametinib for *BRAF*-mutant melanoma with brain metastases [19].

We observed a treatment-related steroid dose reduction in two-third of those patients taking steroids at therapy induction, about half of whom were able to discontinue steroids entirely. A similar trend was noted in the reduction/discontinuation of anticonvulsants and narcotic pain medication. We did not measure intracranial response directly, but note that in the COMBI-MB study population, intracranial response rates were largely equivalent to (if not better than) extracranial response rates [19]. Although our findings represent an imperfect surrogate for intracranial response, they suggest concordance with the COMBI-MB data, and may help to allay doubts that still exist about the ability of these drugs to successfully penetrate the central nervous system [21–23].

A screen of available baseline patient characteristics did not reveal any univariate predictors of PFS or OS in our cohort, but multivariate analysis suggested older age, lower risk location of original lesion, and nodular melanoma to be poor prognostic indicators. This study was not designed for predictive modeling, and these results should be interpreted with care unless validated in a larger cohort.

We report a toxicity profile that reflects previous reports in the literature, with fever, rash, myositis, diarrhea, and infections accounting for most adverse events [24].

Our population was heterogeneous, international, heavily pretreated, and included patients with significant medical co-morbidities. This increases the real-world applicability and generalizability of the results. However, the study was retrospective, nonrandomized, and uncontrolled, therefore unable to provide insight into the relative

efficacy of any particular BRAF/MEK-inhibitor regimen, or compare BRAF/MEK-inhibitors to alternative therapy strategies.

Given the prevalence of brain metastases and *BRAF* mutations in metastatic melanoma, further studies are needed to compare the relative efficacy of available BRAF/MEK-I regimens in this population. In particular, data on the use of vemurafenib/cobimetinib are lacking. Beyond that, it is still unknown whether BRAF/MEK-I should be used alongside or in parallel with brain radiation and/or immunotherapy for patients with brain metastases. It is also unknown how pretreatment with immunotherapy could influence response to targeted therapy, or vice-versa. We hope that further studies can help to elucidate the optimal clinical approach in this population.

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Conflicts of interest

E.L. declares advisory board and speakers honoraria from Bristol-Myers Squibb, Boehringer-Ingelheim, Amgen, Roche, Novartis, and Merck Sharp and Dohme, as well as travel support from Amgen, Boehringer-Ingelheim, Merck Sharp and Dohme, and Novartis. L.Z. has served as consultant or/and has received honoraria from Roche, Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, and Pierre Fabre and travel support from MSD, BMS, Amgen, Novartis, and Pierre Fabre. V.C.A. has received funding from the Euronco Foundation (Zurich, Switzerland) and the Louis Widmer AG (Schlieren, Switzerland). J.M. has received travel grants from MSD and has intermittent advisory roles for Merck/Pfizer. R.D. has received research funding by the University of Zürich from Novartis, Merck Sharp and Dhome, Bristol-Myers Squibb, and Roche and has an intermittent consultant or advisory board relationship with Novartis, Merck Sharp and Dhome, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, and Sun Pharma. S.M.G. has received travel grants and has intermittent advisory roles for BMS, MSD, Novartis, and Roche and has received research support from the University of Zurich and medAlumni. R.J.S. has served on an advisory board for Novartis Pharmaceuticals, has received consulting fees from Roche-Genentech, and is an unpaid advisor to Array Biopharma. For the remaining authors, there are no conflicts of interest.

References

1 American Cancer Society. Cancer Facts & Figures 2017. 2017. Available at: *https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf*. [Accessed 27 April 2018].

2 Bhatia P, Friedlander P, Zakaria EA, Kandil E. Impact of BRAF mutation status in the prognosis of cutaneous melanoma: an area of ongoing research. *Ann Transl Med* 2014; **3**:2.

3 Kim SY, Kim SN, Hahn HJ, Lee YW, Choe YB, Ahn KJ. Metaanalysis of BRAF mutations and clinicopathologic characteristics in primary melanoma. *J Am Acad Dermatol* 2015; **72**:1036–1046.

4 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**:5–29.

5 Ajithkumar T, Parkinson C, Fife K, Corrie P, Jefferies S. Evolving treatment options for melanoma brain metastases. *Lancet Oncol* 2015; **16**:486–497.

6 Goldinger SM, Panje C, Nathan P. Treatment of melanoma brain metastases. *Curr Opin Oncol* 2016; **28**:159–165.

7 Ray S, Dacosta-Byfield S, Ganguli A, Bonthapally V, Teitelbaum A. Comparative analysis of survival, treatment, cost and resource use among patients newly diagnosed with brain metastasis by initial primary cancer. *J Neurooncol* 2013; **114**:117–125.

8 Cicenas J, Tamosaitis L, Kvederaviciute K, Tarvydas R, Staniute G, Kalyan K, *et al*. KRAS, NRAS and BRAF mutations in colorectal cancer and melanoma. *Med Oncol* 2017; **34**:26.

9 Center for Drug Evaluation and Research. Approved drugs – dabrafenib. Available at: *http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm354477.htm*. [Accessed 20 February 2017].

10 Center for Drug Evaluation and Research. About the Center for Drug Evaluation and Research – Vemurafenib. Available at: *http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm268301.htm*. [Accessed 20 February 2017].

11 Webster RM, Mentzer SE. The malignant melanoma landscape. *Nat Rev Drug Discov* 2014; **13**:491–492.

12 Long GV, Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, Larkin J, *et al*. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015; **386**:444–451.

13 Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, *et al*. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015; **372**:30–39.

14 Center for Drug Evaluation and Research. Approved drugs – trametinib and dabrafenib. Available at: *http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm381451.htm*. [Accessed 20 February 2017].

15 Geukes Foppen M, Boogerd W, Blank C, Haanen JBAG, van Thienen JV, Brandsma D. Neurological benefit of BRAF-inhibition and MEK-inhibition in patients with brain metastases from BRAF-mutated melanoma. *Ann Oncol* 2016; **27** (**Suppl 6**):1141P.

16 Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, *et al*. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012; **379**:1893–1901.

17 Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, *et al*. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**:1087–1095.

18 Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, *et al*. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer* 2014; **50**:611–621.

19 Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, *et al*. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases(COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017; **18**:863–873.

20 Unger JM, Barlow WE, Martin DP, Ramsey SD, Leblanc M, Etzioni R, Hershman DL. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst* 2014; **106**:dju002.

21 Rochet NM, Dronca RS, Kottschade LA, Chavan RN, Gorman B, Gilbertson JR, Markovic SN. Melanoma brain metastases and vemurafenib: need for further investigation. *Mayo Clin Proc* 2012; **87**:976–981.

22 Vaidhyanathan S, Mittapalli RK, Sarkaria JN, Elmquist WF. Factors influencing the CNS distribution of a novel MEK-1/2 inhibitor: implications for combination therapy for melanoma brain metastases. *Drug Metab Dispos* 2014; **42**:1292–1300.

23 Gummadi T, Zhang BY, Valpione S, Kim C, Kottschade LA, Mittapalli RK, *et al*. Impact of BRAF mutation and BRAF inhibition on melanoma brain metastases. *Melanoma Res* 2015; **25**:75–79.

24 Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol* 2015; **7**:122–136.